

### REMARKS

Following entry of this amendment, claims 1, 5-8, 10, 13-22, 30, 35, 36, 39-41, 43, 45, 46, 49-55, 57-60, 62, 66, 68, 70-76, 111-116 and 120-134 will be pending. Claims 1, 7, 8, 10, 13-15, 36, 43, 45, 46, 49, 50, 62, 66, 68, 74-76, 112, 114, 116 and 120-122 have been amended. Claims 123 to 134 have been newly added. Dependent claims 9, 11, 12, 23, 44, 47, 48, 61, 64, 65 and 67 have been canceled, without prejudice to presenting the deleted subject matter in one or more continuation applications.

#### *Rejections Under 35 U.S.C. § 112, Second Paragraph*

In the Office Action dated June 24, 2005, all of the pending claims were rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the term “wherein said minoxidil is present at a concentration which is less than its solubility limit” rendered the claims vague, in that it is not clear as to the concentration of minoxidil in the composition. Applicants respectfully traverse this rejection.

Each of the pending claims requires that minoxidil be present at a concentration of from about 5 to about 8 weight %, based on the total weight of the defined compositions (page 6, lines 2 to 4). Thus, there is clearly no ambiguity as to the concentration of minoxidil that is required in the present compositions. The phrase “wherein said minoxidil is present at a concentration which is less than its solubility limit” imposes a second limitation on the presently defined compositions – the minoxidil must be in solution in the compositions. The Examiner’s attention is directed in this regard to the specification at page 6, lines 13 to 17. Applicants note that, as originally filed, the claims recited the term “substantially solubilized” instead of the phrase objected to by the Examiner, but replaced that term with the present claim language (which reflects the definition for the term “substantially solubilized” as provided in the application) in response to a previous rejection. In view of such teachings, it is submitted that the rejection is improper and should be withdrawn.

Claims 7, 8, 11, 12, 15, 36, 39-41, 43, 46, 47, 50, 57-62, 64, 70-76, 113-116 and 120-122 were also rejected under Section 112, second paragraph, on the grounds that the terms “alcohol”, “polyol”, and “glycol” are indefinite. Applicants respectfully disagree with the Examiner on this point, and submit that these terms are adequately defined such that the

metes and bounds of these terms would readily be understood by those of ordinary skill in the art, once placed in possession of the present application. However, in the interest of advancing prosecution of this application and reducing the issues for any subsequent appeal to the Board, Applicants have amended the claims, *inter alia*, to recite exemplary alcohols, polyols and glycols. Applicants hereby expressly reserve the right to pursue claims which include the terms "alcohol", "polyol" and "glycol" in one or more continuing applications.

Similarly, claims 23 and 61 were rejected on the grounds that the terms "fragrance modifiers" and "oils" were vague and indefinite. Applicants again respectfully disagree with the Examiner on this point, but have deleted these two claims to minimize the pending issues. It should be understood that by taking this action, Applicants are not surrendering coverage of compositions containing any of the additional ingredients recited in claims 23 and 61, nor do Applicants in any way imply or suggest that compositions containing the ingredients recited in dependent claims 23 and/or 61 are not within the scope of the remaining claims.

In view of the foregoing, Applicants respectfully request that the rejections under Section 112, second paragraph, be withdrawn.

### ***Rejections Under 35 U.S.C. § 103***

In the Office Action dated June 24, 2005, the previous rejection of claims 1, 5-7, 8-14, 15-19, 21-23, 30, 35, 62, 64-68, 70-72, 74, 75 and 111 as being obvious over Preuilh (US 6,106,848) in view of Ewers (DE 19613698) and further in view of Pena (US 5,225,189) has been maintained. The combination of these three references, together with additional references (including Samour, Sine, Anton and/or Grollier) are said to render the remaining claims obvious.

As the Examiner correctly notes in the Office Action, Preuilh is directed to oil-in-water emulsions containing a thickening or gelling agent, rather than to *single-phase gels*, which are the subject of the pending claims. The emulsions are said to contain anywhere from 0.0001% to 20% by weight of an active agent that may be selected from a laundry list of active agents that includes minoxidil. The only formulation explicitly set forth in Preuilh is said to contain 0.05% of an unidentified active agent, which corresponds to 1/100<sup>th</sup> of the lowest concentration of minoxidil recited in the presently pending claims.

Pena is directed to single-phase, minoxidil-containing gels. The reference indicates at col. 3, line 19 that in connection with the preparation of a composition composed of three parts, a “second part” is prepared “containing from greater than 0 to 5% minoxidil.” However, as would be apparent to an ordinarily skilled artisan, the final concentration of minoxidil in the disclosed compositions would be less than 5% when this “second part” is combined with the first and third parts, per the teachings in Pena. Moreover, the remaining teachings in Pena identify minoxidil concentrations of only up to 3% (*see* col. 1, Summary of the Invention; cols. 4-6, Examples 1-3; col. 6, claim 1). In addition, the only thickening agent described in Pena is the carbomer Carbopol® 934P.

The obviousness rejections set forth in the office action further rely on Ewers as a “bridge” that is said to motivate one of skill in the art to modify the oil-in-water emulsion of Preuilh in accordance with Pena. Applicants reiterate, once again, that not only is this combination improper since a proper motivation to combine the cited references has not been established, but that even if the cited references were combined, any proper combination would not provide the claimed invention or render the claimed invention obvious.

With regard to the lack of motivation to combine, Applicants again submit that Ewers cannot properly be used to “bridge” Preuilh and Pena. It is asserted in the Office Action that Ewers represents a general teaching that thickened oil-in-water emulsions and single-phase gels are equivalent and interchangeable. As acknowledged in the Supplemental Declaration of Dr. Pena dated April 11, 2005 (the “Supplemental Pena Declaration”), Ewers identifies several delivery forms which are disclosed as being suitable for a particular esterified estrogen derivative. However, one of ordinary skill in the art would not interpret Ewers to be a teaching that such delivery forms are equivalent and/or interchangeable *generally* (Supplemental Pena Declaration, ¶ 14). An ordinarily skilled artisan readily would readily recognize that different delivery vehicles and delivery forms may lead to drastically different bioavailability and therapeutic effect, as shown, for example, in the text quoted from Remington’s Pharmaceutical Sciences (Supplemental Pena Declaration, ¶ 14). Thus, it is submitted that reliance on Ewers as a “bridge” to establish a motivation to combine the Preuilh and Pena references is inappropriate.

Moreover, Preuilh is directed to the preparation of oil-in-water emulsions, and only mentions minoxidil in connection with a laundry list of possible active agents. The Office

Action fails to provide any indication as to why one of ordinary skill in the art would consult Preuilh and use that as a starting point for preparing high concentration, single-phase minoxidil gels that are the subject of the claimed invention. Even if the ordinarily skilled artisan did start with Preuilh, and desired to modify the disclosed emulsions to provide a single-phase gel formulation, the Office Action fails to indicate why the artisan would include an emulsifier in the modified formulation, when there is no need for an emulsifying agent in a single-phase system. Since Preuilh teaches that the only use for Pemulen TR-2 in the composition is as an emulsifier (indeed, teaching other ingredients, such as Carbopol 934 and hydroxypropylmethylcellulose, as gelling and/or thickening agents), one of skill in the art would have no motivation to include Pemulen TR-2 when modifying the composition to produce a single-phase gel. It is submitted that absent the benefit of impermissible hindsight from the teachings in the present application, the ordinarily skilled artisan would, at best, elect to use a material that is disclosed in Preuilh as being a thickening or gelling agent, such as Carbopol 934 or the exemplified hydroxypropylmethylcellulose, in an effort to "gel" the proposed composition. It is further submitted that even if the artisan further consulted Pena, as has been done in crafting the obviousness rejections, the motivation to use the carbomer Carpopol® 934P, which is described as an appropriate thickening/gelling agent in both Preuilh and Pena, would be even stronger. The Office Action continues to ignore this fact.

The Office Action also ignores the evidence in the present application that shows that Carpopol® 934P, as taught by both Preuilh and Pena, fails to produce a satisfactory 5% minoxidil gel. As shown in Example IV in the present application, when Carpopol® 934P was utilized as the thickening agent in a 5% minoxidil gel, both the minoxidil and Carpopol® 934P precipitated out of solution. Despite this clear evidence, the Office Action inexplicably continues to assert that Pena teaches a 5% single-phase minoxidil gel. Applicants respectfully submit that it is a fundamental tenet of patent law that a reference must enable the subject matter that is being relied upon as a basis for an art rejection. The evidence from Example IV shows that Pena does NOT enable a 5% single-phase minoxidil gel, and the Patent Office has failed to adequately address this established deficiency in Pena.

Moreover, Applicants have submitted evidence that shows that Preuilh fails to even adequately describe a satisfactory 3% emulsion gel. When Dr. Pena prepared the formulation of Example 1 from Preuilh, utilizing 3% minoxidil as the active agent, the resulting

composition proved to be unstable. Nevertheless, the Patent Office continues to rely on Preuilh as teaching “stable compositions comprising up to 20% of active agent such as minoxidil”, despite Applicants’ established evidence to the contrary.

Applicants respectfully submit that the Office Action has failed to consider all of the evidence of record, evidence that clearly defeats any *prima facie* showing of the obviousness of the claimed subject matter, if such a case of obviousness was ever properly made. In essence, the obviousness rejections set forth in the Office Action presume the skilled artisan would do the following in an effort to prepare improved compositions of minoxidil:

- (1) consult Preuilh and select minoxidil from the laundry list of active agents;
- (2) select a minoxidil concentration of about 5% to about 8%, even though Preuilh only sets forth a composition with 0.05% of an unidentified active agent, and experimental evidence shows that a composition prepared in accordance with Preuilh’s teachings, containing as little as 3% minoxidil, fails as being unstable;
- (3) consult Ewers, a reference directed to formulations for the transmucosal delivery of an estrogen derivative and having nothing whatsoever to do with minoxidil, and conclude from that reference that instead of using the Preuilh oil-in-water emulsion, a single-phase gel should be used;
- (4) on the basis of Ewers’ purported “guidance,” consult Pena, since it teaches single-phase minoxidil gels;
- (5) upon finding that the composition taught by Pena fails when prepared with about 5% minoxidil, go back to the failed Preuilh teaching and select one of the ingredients described therein as an emulsifying agent, instead of one of the numerous thickening or gelling agents described therein, to “gel” the formulation, even though there is no indication in Preuilh as to why one would include an emulsifying agent when there are no dissimilar phases to emulsify; and
- (6) somehow rely on additional unspecified “skill in the art” to make it all transform into a pharmaceutically elegant product, since none of

Preuilh, Ewers and Pena teaches how to make a pharmaceutically satisfactory composition containing about 5% minoxidil.


Applicants respectfully submit that a proper obviousness rejection requires something more than the foregoing, as asserted in the Office Action.

Applicants have shown that neither Preuilh nor Pena provides a suitable starting point for a proper *prima facie* obviousness case. Simply put, no proper combination of these references, when viewed in the context of the experimental evidence provided by Applicants in the Pena Declarations and Example IV of the application as filed, with or without the "bridge" of Ewers, would lead one to the single-phase gels of the present invention.

### **Conclusion**

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections of pending claims 1, 5-8, 10, 13-22, 30, 35, 36, 39-41, 43, 45, 46, 49-55, 57-60, 62, 66, 68, 70-76, 111-116 and 120-134 and an early notice of allowance are requested respectfully.

Date: August 19, 2005

  
S. Maurice Valla  
Registration No. 43,966

Woodcock Washburn LLP  
One Liberty Place - 46th Floor  
Philadelphia PA 19103  
Telephone: (215) 568-3100  
Facsimile: (215) 568-3439